

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF WISCONSIN

THIRD WAVE TECHNOLOGIES, INC.,

Plaintiff,

v.

STRATAGENE CORPORATION,

Defendant.

OPINION AND
ORDER

04-C-680-C

In this civil action, plaintiff Third Wave Technologies, Inc. contends that defendant Stratagene Corporation infringed claims 1, 5, 7, 12 and 14 of plaintiff's U.S. Patent No. 6,348,314 (the '314 patent) and claim 16 of plaintiff's U.S. Patent No. 6,090,543 (the '543 patent), both of which relate to cleavage of nucleic acids, by making, using, importing, offering for sale and selling its FullVelocity™ products. Plaintiff seeks declaratory, injunctive and monetary relief under 35 U.S.C. § 271. Defendant asserts four counterclaims, seeking declarations of non-infringement and invalidity of the two patents. The case is before the court on plaintiff's motion for summary judgment on the issue of infringement. Jurisdiction is present. 28 U.S.C. §§ 1331 and 1338(a).

Although the parties have raised a host of arguments, their primary dispute is whether the mutant *Pfu* polymerase enzyme employed by defendant's products prevents the two oligonucleotides claimed in the patents from defining contiguous regions on the target nucleic acid, as required in both patents. Defendant argues that the physical space occupied by the polymerase prevents the establishment of contiguity. Although plaintiff has submitted evidence suggesting that the *Pfu* polymerase dissociates from the structure prior to cleavage, it has not attempted to show that the physical space once occupied by the polymerase left vacant after dissociation fills in or closes up, either by the addition of new nucleotides or by re-annealing of the oligonucleotide that the polymerase had displaced. Because I find the evidence on the question of contiguity to be inconclusive, plaintiff's motion will be denied.

From the parties' proposed findings of fact, I find the following to be material and undisputed.

UNDISPUTED FACTS

A. The Parties

Plaintiff Third Wave Technologies is a Delaware corporation with its principal place of business in Madison, Wisconsin. Plaintiff is the owner by valid assignment of U.S. Patent No. 6,348,314 (the '314 patent) and U.S. Patent No. 6,090,543 (the '543 patent).

Defendant Stratagene Corporation is a Delaware corporation with its principal place of business in La Jolla, California. Defendant manufactures and sells biological products including FullVelocity™ QPCR Master Mix and FullVelocity™ QRT-PCR Master Mix, both of which are designed for probe-based detection of nucleic acids. (I will refer to the FullVelocity™ QPCR Master Mix and FullVelocity™ QRT-PCR Master Mix collectively as the “FullVelocity™ products,” ignoring the other products in defendant’s FullVelocity™ line that are not accused of infringement.) On September 15, 2004, plaintiff brought this suit against defendant, contending that the FullVelocity™ products infringe both the ‘314 and ‘543 patents.

B. Background Technology

With the exception of bacteriophage, DNA viruses and RNA viruses, all living things contain genetic information in one or more long molecules known as a chromosomes. Each chromosome comprises a number of subunits called genes, which are composed of deoxyribonucleic acid, DNA, that encodes the information necessary for cells to reproduce and to produce specific proteins critical to sustaining life. On the molecular level, DNA consists of two long chains or strands that wrap around each other in a shape commonly referred to as a double helix, which can be visually conceptualized as a twisted ladder. In diameter, the double helix is approximately 70 angstroms long, with an angstrom being one

hundred millionth of a centimeter.

The building blocks for each strand are called nucleotides, each consisting of a sugar group, a phosphate group and a base. The sugar and phosphate groups are constant and form the sides of the ladder. The rungs of the ladder are made of pairs of bases, one from each of the two DNA strands. There are four different bases found in DNA: adenine, or A; guanine, G; cytosine, C; and thymine, T. Nucleotides are identified according to the type of base they contain. Each rung is separated by 3.4 angstroms. Typically, an oligonucleotide is defined as a single strand of DNA (not in a double helix) made up of a few nucleotides; the term polynucleotide is commonly used to refer to a strand with many nucleotides.

A single strand of DNA can be graphically represented by listing the order of bases in that strand, e.g., A-T-G-C-C-G-T-A. The genetic information contained in each DNA molecule is conveyed according to the sequence of nucleotides. Because particular errors in genetic sequences have been correlated with a number of significant diseases, much scientific research has been devoted to identifying and detecting nucleotide sequences that cause disease or affect the treatment of disease.

1. Hybridization

The process by which two strands of DNA come together is called hybridization and can be visualized as the closing of a zipper. Hybridization occurs under certain reaction

conditions when the sequences of bases in two strands of DNA are sufficiently complementary. For reasons having to do with the chemical composition of each of the bases, A prefers to pair with its complement T and C prefers to pair with its complement G. Thus, a strand of DNA with the sequence AACGATGC will prefer to hybridize with a second strand containing the sequence TTGCTACG. A can also pair with the base uracil, U, which is found in nature in ribonucleic acid (RNA). RNA is similar to DNA except in the type of sugar found in each nucleotide and the inclusion of the base uracil (U) in place of thymine (T). In artificial systems, U can be used in DNA instead of T. The phenomenon of complementary base pairing makes it possible to infer the order of nucleotides found on one strand of DNA from the order of nucleotides on the other side. In other words, if the sequence of one strand of DNA is known, the sequence on a fully complementary strand can be deduced. The known sequence is referred to as the probe, the unknown sequences is called the target.

Each strand of DNA has two ends: a 5' end (pronounced "five prime") and a 3' end (pronounced "three prime"). The sugar group in each nucleotide has a 5' hydroxyl group and a 3' hydroxyl group. The 3' hydroxyl group of one nucleotide connects to the 5' hydroxyl group of the adjoining sugar. At one end of a DNA strand is a nucleotide with an unconnected 5' hydroxyl group and at the other end, a nucleotide with an unconnected 3' hydroxyl group. The end of a DNA strand with an unconnected 5' hydroxyl group is the 5'

end and the opposite end is the 3' end. The two strands making up a double helix hybridize in “anti-parallel” fashion. This means that if one were to draw an arrow from the 3' end toward the 5' end for each of the two strands, the two arrows would be pointing in opposite directions. By convention, a feature on a DNA strand that is in the 5' direction from a second feature on the same strand is referred to as being “upstream” of the second feature; a feature in the 3' direction is referred to as being “downstream” of the second feature. Thus, when two oligonucleotides hybridize to a single nucleic acid molecule so that the 5' end of one oligonucleotide is upstream of the 5' end of the other, the first oligonucleotide is known as the “upstream oligonucleotide” and the other as the “downstream oligonucleotide.”

2. DNA replication and polymerases

When a cell reproduces or divides, its DNA copies itself in a process called DNA replication. During replication, the two strands of DNA separate from each other through a process referred to as denaturation and each serves as a template for a newly synthesized complementary strand of DNA. DNA replication is facilitated by enzymes, which are protein-based molecules that catalyze certain biochemical reactions, including the replication and manipulation of genetic information. Different types of enzymes vary in the type of reactions they catalyze, the temperature at which they function and the substances upon which they react. Enzymes that work at elevated temperatures are said to be thermostable.

Of particular importance in DNA replication are polymerase enzymes. Polymerases create DNA strands that are complementary to a template strand by generating one complementary nucleotide at a time. Polymerization takes place in a pocket sometimes called an active site within the polymerase. Occasionally, polymerases insert a non-complementary nucleotide, which is known as a mismatch. Polymerization occurs in a directional manner: a polymerase moves upstream along the target and adds nucleotides to the 3' end of the newly created strand. When certain types of polymerase enzymes encounter an oligonucleotide annealed to the template, they displace this oligonucleotide one nucleotide at a time to make way for the extending strand.

3. DNA cleavage and nucleases

A nuclease enzyme can identify particular base sequences and cleave, or cut these sequences at specific places. Nuclease enzymes are capable of cleaving the bond between two adjacent nucleotides located on the same strand of DNA. If a nuclease removes one or more nucleotides from the 5' end of a nucleic acid molecule, it is said to have "5' to 3' activity"; nucleases having 5' to 3' activity are called 5' nucleases. Conversely, if a nuclease removes a nucleotide from the 3' end of a nucleic acid molecule, it is said to have "3' to 5' activity." A nuclease that can remove a nucleotide from the end of a nucleic acid strand is said to have "exonuclease" activity, whereas a nuclease that can remove a nucleotide from the middle of

a nucleic acid strand has “endonuclease” activity. Structure-specific enzymes can identify specific nucleic acid structures and cleave those structures at specific sites. Some polymerases, such as the *E. coli* DNA Pol I and the *Taq* polymerase, are able to both synthesize and cleave DNA. Enzymes with both capabilities are said to have both “polymerase” activity and “nuclease” activity.

C. The Patents

1. Background technology

Both plaintiff’s ‘543 and ‘314 patent claim methods for detecting the presence of a target nucleic acid molecule by forming nucleic acid cleavage structures and cleaving them in a site-specific manner so as to release distinct detectable non-target cleavage products. When two oligonucleotides are mixed under certain reaction conditions with a target nucleic acid having a particular base sequence, the two oligonucleotides will hybridize to the target in a specific manner, creating a cleavage structure. (The cleavage structure claimed in the ‘543 patent differs from that claimed in the ‘314 patent.) When these cleavage structures are cleaved by a cleaving means that is mixed with the target and two oligonucleotides, they release the detectable non-target cleavage products. The detection of these non-target cleavage products signifies the existence of the particular base sequence in the target strand. Identifying specific target sequences can be used in forensics or to identify and study

genetically-based diseases and viral or bacterial infections.

2. The '543 patent

Claim 16 is the only claim in the '543 patent implicated in this case. It reads as follows:

16. A method of detecting the presence of a target nucleic acid molecule by detecting non-target cleavage products comprising:

a) providing:

I) a cleavage means,

ii) a source of target nucleic acid, said target nucleic acid having a first region, a second region and a third region, wherein said first region is downstream from said second region and wherein said second region is contiguous to and downstream from said third region;

iii) first and second oligonucleotides having 3' and 5' portions, wherein said 3' portion of said first oligonucleotide contains a sequence complementary to said third region of said target nucleic acid and wherein said 5' portion of said first oligonucleotide and said 3' portion of said second oligonucleotide each contain sequence fully complementary to said second region of said target nucleic acid, and wherein said 5' portion of said second oligonucleotide contains sequence complementary to said first region of said target nucleic acid;

b) mixing, in any order, said cleavage means, said target nucleic acid, said first oligonucleotide and said second oligonucleotide to create a reaction mixture under reaction conditions such that at least said 3' portion of said first oligonucleotide is annealed to said target nucleic acid and wherein at least said 5' portion of said second oligonucleotide is annealed to said target nucleic acid so as to create a cleavage structure and wherein cleavage of said cleavage structure occurs to generate non-target

cleavage products, each non-target cleavage product having a 3'-hydroxyl group; and
c) detecting said non-target cleavage products.

The following is a schematic depiction of the cleavage structure described in claim 16:

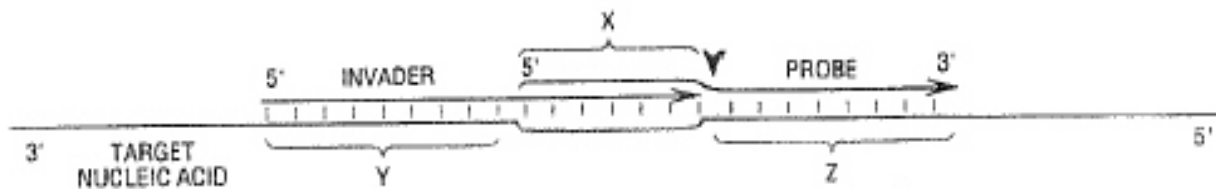


Illustration No. 1

The section of the target nucleic acid labeled “Y” depicts the “first region,” the section labeled “X” depicts the “second region” and the segment labeled “Z” depicts the “third region.” The oligonucleotide labeled “probe” represents the “first oligonucleotide” and the other labeled “invader” represents the “second oligonucleotide.”

Describing claim 16 in terms of this depiction, the 5' portion of the invader must contain a sequence complementary to region Y; both the 3' portion of the invader and the

5' portion of the probe must contain a sequence *fully* complementary to region X; and the 3' portion of the probe must contain a sequence complementary to region Z. Regions X and Z must be contiguous. The cleavage structure is created when the 3' portion of the probe anneals to region Z, the 5' portion of the invader anneals to region Y and the 5' end of the probe and the 3' end of the invader overlap in region X.

Once the cleavage structure is formed, it can be cleaved by the cleavage means. The cleavage process generates non-target cleavage products. Specifically, the non-target cleavage product of claim 16 is derived from the 5' end of the first oligonucleotide (the probe) when it is cleaved in the cleavage structure; it is not derived from the target nucleic acids. The cleavage fragments from the 5' end of the first oligonucleotide have a 3' hydroxyl group.

3. The '314 patent

Claim 1 of the '314 patent reads as follows:

I. A method for detecting the presence of a target nucleic acid molecule by detecting non-target cleavage products comprising:

a) providing:

I) a cleavage agent;

ii) a source of target nucleic acid, said target nucleic acid comprising a first region and a second region, said second region downstream of and contiguous to said first region;

iii) a first oligonucleotide, wherein at least a portion of said first oligonucleotide is completely complementary to said first portion of said first target nucleic acid;

iv) a second oligonucleotide comprising a 3' portion and a 5' portion, wherein said 5' portion is completely complementary to said second portion of said target nucleic acid;

b) mixing said cleavage agent, said target nucleic acid, said first oligonucleotide and said second oligonucleotide to create a reaction mixture under reaction conditions such that at least said portion of said first oligonucleotide is annealed to said first region of said target nucleic acid and wherein at least said 5' portion of said second oligonucleotide is annealed to said second region of said target nucleic acid so as to create a cleavage structure, and wherein cleavage of said cleavage structure occurs to generate non-target cleavage product; and

c) detecting the cleavage of said cleavage structure.

Claim 1 contains no requirement that the 3' portion of the second oligonucleotide be complementary to the target nucleic acid. It does require that the non-target cleavage products be derived from the first oligonucleotide in the cleavage structure and not from the target nucleic acid.

Claims 5 and 7 depend on claim 1. They read as follows:

5. The method of claim 1, wherein said detecting the cleavage of said cleavage structure comprises detection of fluorescence.

. . .

7. The method of claim 1, wherein said detecting the cleavage of said cleavage structure comprises detection of fluorescence energy transfer.

Claims 12 and 14 are dependent on claim 11, which claims "[t]he method of claim

1, wherein said cleavage agent comprises a structure-specific nuclease.” Claims 12 and 14 read as follows:

12. The method of claim 11, wherein said structure-specific nuclease comprises a thermostable structure-specific nuclease.

14. The method of claim 13, wherein said 5'-nuclease comprises a thermostable 5'-nuclease.

4. Terminology

As used in these claims, the term “contiguous” means that there are no nucleotides between the relevant sections or regions; “annealed” means the pairing of complementary nucleic acid molecules via hydrogen bonding to form a duplex, or double stranded base pair or base-paired region of nucleic acid; “complementary” refers to bases that are related by base pairing rules; and “completely complementary” means that each and every nucleotide of a completely complementary portion can base pair to each and every corresponding nucleotide of the target sequence. The common and ordinary meaning of the term “providing” is “to furnish, supply or to make available.” Neither patent requires that the reagents be provided in any particular manner. Providing can take place either before or during the mixing step; however, all reagents must be provided before mixing is complete.

In both patents, the term “oligonucleotide” is defined in the claim specifications as “a molecule comprised of two or more deoxyribonucleotides or ribonucleotides, preferably

at least 5 nucleotides, more preferably at least about 10-15 nucleotides and more preferably at least about 15 to 30 nucleotides. The exact size will depend on many factors, which in turn depends on the ultimate function or use of the oligonucleotide.” ‘543 Pat., col.18, lns. 58-6; ‘314 Pat., col. 16, lns. 10-14. Further, the specifications state that “the oligonucleotide may be generated in any manner, including chemical synthesis, DNA replication, reverse transcription, or a combination thereof.” ‘543 Pat., col.18, lns. 64-67; ‘314 Pat., col. 16, lns. 16-19. One of ordinary skill in the art would understand that these techniques require unique reaction conditions.

The term “primer” means “an oligonucleotide [] capable of acting as a point of initiation of synthesis when placed under conditions in which primer extension is initiated.” ‘543 Pat., col. 19, lns. 21-25; ‘314 Pat., col. 16, lns. 39-43. The specifications make clear that a primer may occur naturally or may be produced synthetically. ‘543 Pat., col. 19, lns. 25-26; ‘314 Pat., col. 16, lns. 43-44. A “probe oligonucleotide” is defined as “an oligonucleotide which interacts with a target nucleic acid to form a cleavage structure in the presence or absence of an invader oligonucleotide.” ‘543 Pat., col. 21, lns. 27-30; ‘314 Pat., col. 18, lns. 47-50. “When annealed to the target nucleic acid, the probe oligonucleotide and target form a cleavage structure and cleavage occurs within the probe oligonucleotide.” ‘543 Pat., col. 21, lns. 30-32; ‘314 Pat., col. 18, lns. 50-52.

As defined in the specifications, the term “cleavage means” “refers to any means

which is capable of cleaving a cleavage structure, including but not limited to enzymes.” ‘543 Pat., col. 20, lns. 55-57; ‘314 Pat., col. 18, lns. 6-8. Further, the specifications state that “[t]he cleavage means of the invention cleave a nucleic acid molecule in response to the formation of cleavage structures; it is not necessary that the cleavage means cleave the cleavage structure at any particular location within the cleavage structure.” ‘543 Pat., col. 21, lns. 2-7; ‘314 Pat., col. 18, lns. 20-25. These definitions make it clear that “cleavage means” may include “native DNAPs having 5' nuclease activity (e.g., *Taq* DNA polymerase, *E. coli* DNA polymerase I) and, more specifically, modified DNAPs having 5' nuclease but lacking synthetic activity.” ‘543 Pat., col. 20, lns. 58-61; ‘314 Pat., col. 18, lns. 9-12.

The specifications identify certain types of enzymes that may act as a “cleavage means.” Portions of the specifications state that “[i]n one embodiment, the means for cleaving is a cleaving enzyme comprising 5' nucleases derived from thermostable DNA polymerases.” ‘543 Pat., col. 5-6, lns. 67-2; ‘314 Pat., col. 8, lns. 24-27. Later, the specifications provide that

The 5' nucleases of the invention are capable of cleaving this structure but are not capable of polymerizing the extension of the 3' end of the first oligonucleotide. The lack of polymerization activity is advantageous as extension of the first oligonucleotide results in displacement of the annealed region of the second oligonucleotide and results in moving the site of cleavage along the second oligonucleotide. If polymerization is allowed to occur to any significant amount, multiple lengths of cleavage product will be generated. A single cleavage product of uniform length is desirable as this cleavage product initiates the detection reaction.

'543 Pat., col. 29, lns. 15-26; '314 Pat., col. 26, lns. 10-21.

The specifications make clear that the cleavage means is not restricted to enzymes having solely 5' nuclease activity. '543 Pat., col. 21, lns. 8-9; '314 Pat., col. 18, lns. 26-27. "The cleavage means may include nuclease activity provided from a variety of sources including the Cleavase.RTM. enzymes, the FEN-1 endonucleases (including RAD2 and XPG proteins), *Taq* DNA polymerase and E. coli DNA polymerase I." '543 Pat., col. 21, lns. 9-13; '314 Pat., col. 18, lns. 27-31. Another portion of the specifications provides that in a different embodiment, "the cleavage means is a structure-specific nuclease; particularly preferred structure-specific nucleases are thermostable structure-specific nucleases." '543 Pat. col. 8, lns. 23-26; '314 Pat., 8, lns. 24-27. "Structure-specific nucleases" are defined as "enzymes which recognize specific secondary structures in a nucleic molecule and cleave these structures." '543 Pat., col. 20-21, lns. 66-2; '314 Pat., col. 18, lns. 17-20.

Both specifications specify that the term "hybridization" "is used to refer to the pairing of complementary nucleic acids." '543 Pat., col. 17, lns. 53-54; '314 Pat., col. 15, lns. 3-4. In addition, they state that "[h]ybridization' methods involve the annealing of a complementary sequence to the target nucleic acid." '543 Pat., col. 19., lns. 41-42; '314 Pat., col.16, lns. 60-61.

The "target nucleic acids" may be obtained using standard molecular biological techniques, including isolation from a tissue sample, tissue culture cells or samples

containing bacteria and or viruses. ‘543 Pat., col. 38, lns. 10-14; ‘314 Pat., col. 35, lns. 5-10. They “may also be transcribed in vitro from a DNA template or may be chemically synthesized or generated in a PCR [polymerase chain reaction].” ‘543 Pat., col. 38, lns. 14-16; ‘314 Pat., col. 35, lns. 10-12.

One of ordinary skill in the art would understand that the “mixing” would occur under specific, appropriate reaction conditions to allow the claimed reagents to form a cleavage structure. One of ordinary skill in the area would also understand that the conditions would depend on the particular embodiment of the claimed method. If a polymerase chain reaction is used to generate an oligonucleotide or a target nucleic acid, one of ordinary skill in the art would know that the reaction conditions would include a change in temperature.

5. Third Wave Technologies, Inc. v. EraGen Biosciences, Inc., 02-C-507-C

In Third Wave Technologies, Inc. v. EraGen Biosciences, Inc., 02-C-507-C, I construed certain terms found in claim 16 of the ‘543 patent and claim 14 of the ‘314 patent. In an order entered March 18, 2003, I held that in both claims, reagents may be provided in any manner before or during the mixing step. In other words, if the cleavage means, target nucleic acid and first and second oligonucleotides are provided before mixing is complete, then the requirements for the providing step have been satisfied. I noted that

“there is no language in the claim requiring any of the ingredients to be fully formed when they are added to the mix” and that “the patents do not differentiate between methods of creating oligonucleotides inside or outside the mix, before or during the mixing step.”

In addition, I defined the term “complementary” as referring to “bases that are related by the base pairing rules” that are not limited to bases that hydrogen bond in a standard “Watson-Crick” fashion” and that “completely complementary” means that “every base in a nucleotide sequence is ‘complementary.’” Finally, I concluded that the term “non-target cleavage products” means products of a cleavage reaction that are derived from the 5' portion of the first oligonucleotide.

6. Prior art

a. Gelfand art

The prior art for both the ‘543 and ‘314 patents includes U.S. Patent No. 5,210,015 (the ‘015 patent) and U.S. Patent No. 5,487,972 (the ‘972 patent) (collectively, “the Gelfand art”). In the Gelfand art, a polymerase enzyme was used to extend a primer in the presence of a probe that was base-paired to the template in front of (downstream of) the extended primer. This polymerase extension resulted in cleavage of the probe and detection of cleavage products. The enzyme used throughout the examples in the Gelfand art is *Taq* polymerase. The United States Patent and Trademark Office determined that the Gelfand

art anticipated claim 26 in plaintiff's application for U.S. Patent No. 5,846,717. (Both the '543 patent and the '314 patents claim priority from the '717 patent and specifically, claims 1 and 19 of the '717 patent claim the same structure as claim 16 in the '543 patent except that claims 1 and 19 require that "the combined melting temperature of said complementary regions within said 5' and 3' portions of said first oligonucleotide when annealed to said target nucleic acid is greater than the melting temperature of said 3' portion of said first oligonucleotide.")

In response, plaintiff explained that its claim specifies a cleavage structure where the two oligonucleotides overlap in their hybridization to the target whereas the Gelfand patent specifies that the two oligonucleotides be "adjacent" to one another, meaning that the two oligonucleotides may be located anywhere from zero to twenty nucleotides apart. Thus, plaintiff argued, "adjacent" does not encompass overlapping oligonucleotides. The examiner subsequently withdrew the rejection. During plaintiff's prosecution of the '543 patent, plaintiff emphasized again that in the Gelfand art, there is no overlap in the regions of complementarity of the two oligonucleotides.

b. Lyamichev and Dahlberg

The United States Patent and Trademark Office rejected as obvious several of the claims in plaintiff's application for the '543 patent, including claim 16 in view of Lyamichev

et al. (Science 260:778-783 (May 1993)) and Dahlberg *et al.* U.S. Patent No. 5,422,253.

In plaintiff's response, it depicted the cleavage structures in Lyamichev and the '253 patent as having the following structures:

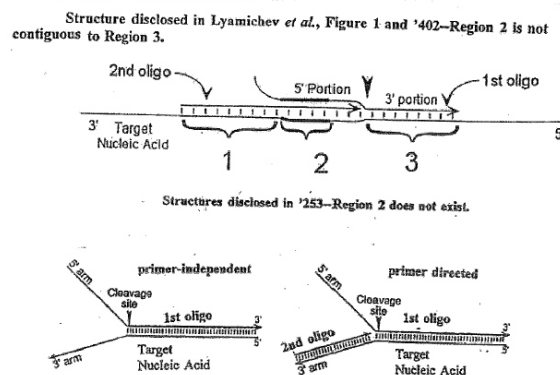


Illustration No. 2

Plaintiff pointed out that in contrast to what its own patents claim, region 2 and region 3 are not contiguous in the structure disclosed in Lyamichev and the '253 patent; the two regions are separated by nucleotides. In addition, plaintiff added language to claim 16 specifying the need for contiguity between regions 2 and 3.

The patent examiner responded that “the amendment of the claims to recite that the regions are contiguous does not overcome the prior art for the following reasons. Webster’s II dictionary defines contiguous as 1) sharing a boundary or edge or 2) nearby; adjacent. Therefore, the regions of the target nucleic acid of the prior art meet the definition of being contiguous as is now claimed.” However, the examiner added, “the prior art does not teach

or suggest or provide sufficient motivation and guidance to obtain the instantly claimed invention wherein the oligonucleotides each contain a region fully complementary to the target” Plaintiff amended its application to specify that the 5' portion of the first oligonucleotide and the 3' portion of the second oligonucleotide “each contain a sequence fully complementary to said second region” of the target nucleic acid. The examiner emphasized this amended language in allowing the claim.

c. The ‘311 and ‘402 patents

The prior art for the ‘543 patent includes U.S. Patent No. 5,541,311 (the ‘311 patent) and U.S. Patent No. 5,614,402 (the ‘402 patent). The Patent and Trademark Office rejected claims 16-18 of the ‘543 patent as obvious in view of the ‘311 patent and the ‘402 patent. Although the examiner mistakenly believed that the ‘311 patent and the ‘402 patent did not teach the generation of non-target cleavage products having a free hydroxyl (-OH) group at the 3' terminus, she contended nevertheless that it would have been obvious to use the cleavage structures in a method to obtain non-target cleavage products. In its response, plaintiff argued that neither the ‘311 patent nor the ‘402 patent disclosed a 5' portion of the downstream oligonucleotide that is complementary to a second region of the target.

d. Lundquist

Included in the list of approximately 168 references listed in plaintiff's application for the '314 patent was the publication Lundquist *et al.*, *Transient generation of displaced single-stranded DNA during nick translation*, 31 CELL 1982, at 53-60. The article discloses a method for detecting cleavage of the following cleavage structure by *E. coli* DNA polymerase I:

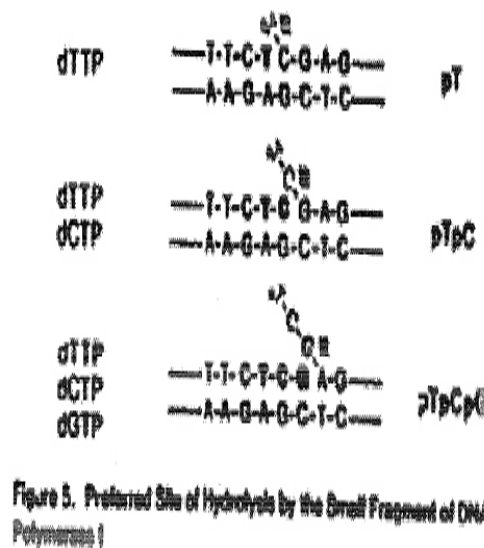


Illustration No. 3

In its information disclosure statement, plaintiff distinguished the references it had listed, noting that “[u]nlike the presently claimed invention, these references do not disclose methods for detecting target nucleic acids based on the cleavage of invasive cleavage structures (e.g. using cycling reactions).” The ‘314 patent specification provides that “[a]n

invasive cleavage structure supports cleavage of the probe in a region that, in the absence of an upstream oligonucleotide, would be expected to be basepaired to the target nucleic acid.” ‘314 Pat., col. 40, lns. 12-15. Plaintiff did not cite the Lundquist article in its application for the ‘543 patent.

D. The FullVelocity™ Products

Defendant’s two FullVelocity™ products at issue, the QPCR Master Mix and the QRT-PCR Master Mix, are designed for the probe-based detection of target nucleic acid molecules. Both are designed to detect the presence of a target nucleic acid and have been used for that purpose. Defendant has offered for sale and sold these products with corresponding instruction manuals to parties in the United States starting in 2004. In 2004, it sold 244 units for over \$110,000. It has made product information and instruction manuals available on the internet since at least April 8, 2004. Defendant intends that its customers use the FullVelocity™ products in the manner set forth in the instruction manuals; defendant has stipulated that the products have no other substantial use; and it informs its customers in its manuals that the products “may not be used in any manner other than as provided herein.” At least two of its customers have used the FullVelocity™ products to detect the presence of target nucleic acids. The QRT-PCR Master Mix involves the same process for detecting target nucleic acid as is used in the QPCR Master Mix plus an

additional step of converting RNA into complementary DNA (cDNA).

1. Reagents included with FullVelocity™ products

Defendant's products contain reagents used for polymerase chain reaction amplification and probe-based detection of a target nucleic acid. Both mixes include a buffer, a reference dye and an enzyme formulation comprising two enzymes: a DNA polymerase and a flap endonuclease. This enzyme formulation possesses cleavage activity and can cleave a probe.

The DNA polymerase included in defendant's product is V93R *Pfu* Exo-DNA, which is a mutation of a naturally occurring *Pfu* DNA polymerase, or a "wild type" *Pfu* polymerase, that does not exhibit nuclease activity. During a polymerase chain reaction involving defendant's FullVelocity™ products, this mutant *Pfu* polymerase extends a primer along a target strand by adding bases complementary to the target to the 3' end of the primer. While it is extending the primer, the mutant *Pfu* polymerase is bound to both the target nucleic acid and to the 3' end of the primer. The front end of a *Pfu* polymerase arrives at a nucleotide on the complementary strand before the portion of the polymerase that adds nucleotides. One study has suggested that the front end of a *Pfu* polymerase is approximately 4-6 nucleotides ahead of the last nucleotide added to the 3' end of the primer. When the mutant *Pfu* polymerase encounters a downstream hybridized oligonucleotide, it

will extend the primer so that the 3' end of the extended primer displaces the downstream oligonucleotide. The displaced portion creates an overlapping flap. A *Pfu* polymerase weighs approximately 90,000 Daltons, a unit of measurement corresponding to roughly the weight of a single hydrogen atom.¹

The flap endonuclease supplied in the FullVelocity™ enzyme formulation is *Pfu* FEN-

1. *Pfu* FEN-1 is a thermostable and structure-specific nuclease having 5' nuclease activity.²

¹Defendant has proposed as fact that a *Pfu* polymerase is approximately 70 angstroms in length. It cites evidence showing that *Taq* polymerases are approximately the same weight as *Pfu* polymerases and that the *Taq* polymerase is approximately 70 angstroms in length. Dft.'s PFOF, dkt. #49 at 6-7, ¶¶ 29-33. Defendant has not pointed to any evidence suggesting that *Pfu* and *Taq* polymerases have the same or similar densities. Without such evidence, it is not reasonable to infer that *Pfu* polymerases and *Taq* polymerases have the same or similar lengths. Because the evidence is not sufficient to support a finding that a *Pfu* polymerase is approximately 70 angstroms in length, it cannot support defendant's proposed fact that the *Pfu* polymerase is the length of approximately 20 nucleotides at 3.4 angstroms each. Dft.'s PFOF, dkt. #49, at 7, ¶ 36.

² Defendant attempts to put into dispute plaintiff's proposed finding of fact regarding the structure-specific character of *Pfu* FEN-1 enzymes by citing to David J. Hosfield *et al.*, *Newly Discovered Archaeobacterial Flap Endonucleases Show a Structure-Specific Mechanism for DNA Substrate Binding and Catalysis Resembling Human Flap Endonuclease-1*, 273 THE JOURNAL OF BIOLOGICAL CHEMISTRY, Oct.16, 1998, at 27154, for the proposition that *Pfu* FEN-1 enzymes are sequence-specific. Although defendant does not say so explicitly, I must assume that it means to suggest that structure-specific and sequence-specific qualities are mutually exclusive in nucleases. The article defendant cites does not support this proposition. Although the authors note that a study by John J. Harrington and Michael R. Lieber showed that the *Pfu* FEN-1 enzyme showed very little activity towards a GC-rich flap substrate, they report that the study showed that the *Pfu* FEN-1 enzyme cleaved psuedo-Y substrates readily. *Id.* at 27159. In Harrington and Lieber's account of their study, they concluded that their research had "confirm[ed] that FEN-1 is a DNA structure-specific endonuclease." John J. Harrington & Michael R. Lieber, *The Characterization of a Mammalian DNA Structure-*

Pfu FEN-1 is a thermostable 5' nuclease enzyme capable of cleaving the cleavage structure claimed in claim 16 of the '543 patent and in claim 1 of the '314 patent. In one peer-reviewed study of *Pfu* FEN-1, no cleavage was detected when an invader oligonucleotide was missing or when there was no overlap between two oligonucleotides. The study concluded that "the *Pfu*FEN1 endonuclease requires at least one overlapping nucleotide between the signal and invasive probes to recognize and cleave the displaced 5' end of the signal probe." Victor Lyamichev *et al.*, *Polymorphism Identification and Quantitative Detection of Genomic DNA by Invasive Cleavage of Oligonucleotide Probes*, 17 NATURE BIOLOGY Mar. 1999, at 292. The invader oligonucleotide used to test cleavage with two non-overlapping oligonucleotides has a G base on its 3' terminal while the 3' terminal nucleotides on the invader oligonucleotides used to test cleavage of an overlapping oligonucleotide structures contained an A base. However, the article does not discuss what if any ramifications the particular base found in the 3' terminal nucleotide might have had on the outcome of the experiments. The study

specific Endonuclease, 13 THE EMBO JOURNAL, March 1, 1994, 1235, 1243. In support of this conclusion, Harrington and Leiber noted that (1) "FEN-1 cleaved two different 5' flap structures which were unrelated in sequence"; (2) derivatives of the flap structure lacking an adjacent strand were cleaved far less efficiently than flap structures including the adjacent strand; and (3) branched DNA structures other than a 5' flap, such as Holliday junctions, heterologous loops, Y-junctions, RNA flaps and 3' DNA flaps, were not cleaved by FEN-1. *Pfu* FEN-1 may have some sequence-specific characteristics, but it remains classified with all other FEN-1 enzymes as a structure-specific nuclease. Michael W. Kaiser *et al.*, *A Comparison of Eubacterial and Archaeal Structure-specific 5'-Exonucleases*, 274 THE JOURNAL OF BIOLOGICAL CHEMISTRY, July 23, 1999, at 21387.

showed also that when a *Pfu* FEN-1 endonuclease cleaves an overlapping oligonucleotide structure, the cleavage takes place on the 3' side of the last nucleotide of the upstream oligonucleotide. The *Pfu* FEN-1 enzyme provided in defendant's products has not been altered or mutated.

2. Instructions for FullVelocity™ product use

a. Additional materials required

Defendant instructs its users to supply certain materials for use with its FullVelocity™ products. Those materials include a probe (first oligonucleotide), a primer (second oligonucleotide) and a template including a target nucleic acid. The FullVelocity™ mixes cannot be used to detect a target nucleic acid sequence without a probe, a primer and a source of target nucleic acid. The probe anneals to the target nucleic acid to form part of the structure that is cleaved. Both mixes use probes as reporters and are designed to be used with hydrolysis probes specifically. Hydrolysis probes are oligonucleotides with a DNA backbone that carry one or more labels. Each hydrolysis probe has a fluorophore that is usually located at its 5' end and a quencher that is either internal or on its 3' end. The positions of the fluorophore and the quencher can be reversed. Regardless of their respective positions and regardless whether the probe is annealed to the target or free floating, no fluorescence will be observed from the fluorophore so long as the hydrolysis probe remains

intact. The 5' end of the probe contains a 3' hydroxyl group. When hydrolysis probes that have hybridized to a target nucleic acid are cleaved, they can generate a detectable signal.

A portion of the primer near its 5' end must contain a sequence of nucleotides that is complementary to the target strand and anneals to it. The primer is extended by the *Pfu* polymerase to a point where at least its 3' end is completely complementary to a sequence in the target nucleic acid and a sequence in the probe. (Defendant attempts to put this fact into dispute, arguing that “[t]here is no evidence that the terminal nucleotide on the 3' end of the extended primer is complementary to a sequence on the target nucleic acid that is also complementary to a sequence in the probe because the complex, which is of substantial size, may displace the probe many nucleotides in advance of the addition of nucleotides to the 3' end of the extended primer by the polymerase.” Deft.’s Resp. to Plt.’s PFOF, dkt. #50, at 78-79, ¶ 332. The first and most obvious problem with this argument is that defendant has ignored the evidence in the record supporting plaintiff’s position, namely the expert testimony plaintiff cited in support of its proposed finding of fact. Second, defendant does not cite any evidence suggesting that the displacement process not only moves part of the probe away from the target but also reorders its nucleotide sequence. So long as displacement does not alter base sequences, the probe and target remain “complementary” even though physically moved apart.) A cleavage structure is formed when portions of the probe and the extended primer are annealed to the target nucleic acid.

In addition, defendant's product manuals instruct users to provide experimental gDNA, cDNA, plasmid DNA or RNA and to amplify whichever one of these substances is selected with a polymerase chain reaction. In the event that a user is employing RNA, defendant instructs the user to synthesize a DNA copy of the RNA using reverse transcriptase, which is supplied in the FullVelocity™ QRT-PCR Master Mix kit. This DNA copy, or cDNA, can be used as a template for amplification during PCR.

b. Methodology for using FullVelocity™ mixes

The following figure appears in the instruction manuals for the both QPCR and QRT-PCR:

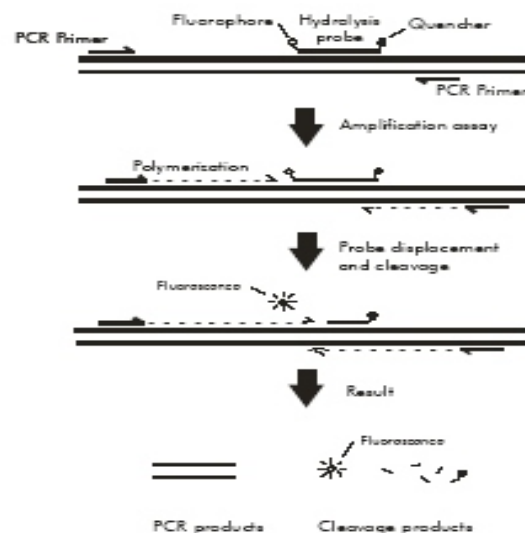


Illustration No. 4

The manuals for both mixes instruct the user to combine water, the QPCR

FullVelocity™ enzyme solution, experimental probes, upstream primers, downstream primers and the reference dye in that order. (In addition, the QRT-PCR mix instructions calls for the addition of StrataScript RT/RNase block enzyme mixture and the FullVelocity enzyme.) The manuals next call for the gentle mixing of these reagents and distribution to PCR reaction tubes. At that point, the user is to add a specified amount of experimental gDNA, cDNA, plasmid DNA or RNA and then gently mix the reaction again. When first added to the mixture, the DNA or RNA is double stranded. Neither the probes nor the primers can hybridize to the DNA or RNA while it remains double stranded. The mixture is then centrifuged briefly before being placed in a thermocycler where it is subject to a series of designated temperature cycles.

The manual for the QPCR Master Mix calls for the mixture to be subject to two minutes at 95°C and then 40 cycles of 10 seconds at 95°C followed by 30 seconds at 60°C. The instructions for the QRT-PCR Master Mix calls for the mixture to be subject to 50°C for 30 minutes, followed by 2 minutes at 95°C and finally, 40 cycles of 10 seconds at 95°C, followed by 30 seconds at 60°C. At 95°C, the double stranded DNA or RNA will undergo denaturation, permitting the oligonucleotides to hybridize to the newly separated single strands. These reaction conditions allow the probe and the extended primer to anneal to the target to form a structure that is cleavable by the *Pfu* FEN-1 endonuclease. The hydrolysis probe anneals to the nucleic acid strand downstream of the primer. The *Pfu* polymerase

extends the 3' end of the primer until it encounters the 5' end of the annealed probe. When the 3' end of the primer encounters the 5' end of the probe, the 5' end of the probe is partially displaced. The displaced 5' end has a sequence that is completely complementary to the portion of the target strand that is completely complementary to the displacing portion of the 3' end of the extended primer.

The reaction conditions permit *Pfu* FEN-1 to cleave the displaced 5' end of the probe. In order to do so, the *Pfu* FEN-1 enzyme must bind to the 3' end of the extended primer. The *Pfu* FEN-1 cannot bind to the 3' end of an extended primer at the same time that the mutant *Pfu* polymerase is bound to the 3' end of the primer. When the reagents are subjected to the reaction conditions, the mutant *Pfu* polymerase dissociates from the extended primer and the probe. Once the mutant *Pfu* polymerase dissociates, *Pfu* FEN-1 binds to the 3' end of the extended primer and cleaves the cleavage structure. When the probe is cleaved, the 5' end that generally contains a fluorophore is separated from the quencher, which is typically on the 3' end or internal. When the fluorophore is disconnected from the quencher, it will release a detectable signal in the form of fluorescence.

In 2004, one of defendant's staff scientists gave a Power Point presentation explaining defendant's QPCR reagent technology. The presentation contained the following depiction under the title "FullVelocity™ Probe Based Chemistry":

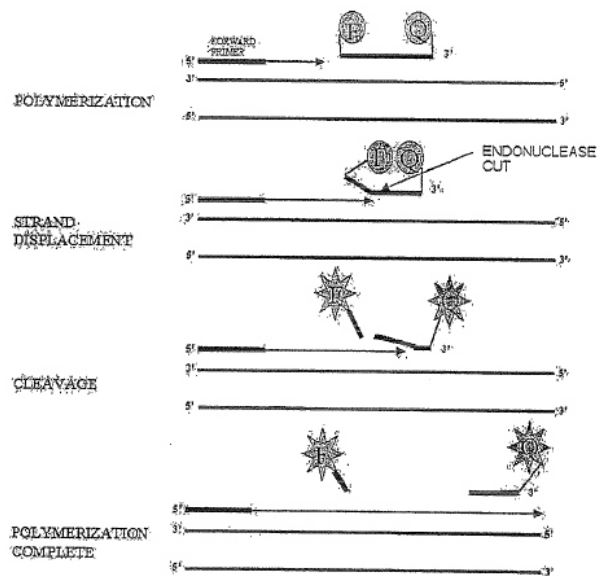


Illustration No. 5

c. Defendant's experiment

Defendant conducted an experiment with the purported goal of determining whether the FullVelocity™ products and process result in the claimed cleavage structures. Although the instruction manuals for both mixes and defendant's senior staff scientist say that the FullVelocity™ products are to be used with complementary probes that anneal to the target nucleic acid, defendant performed its experiment using probes with 29 non-complementary bases on their 5' ends. (Defendant has informed plaintiff of its intention to change its instructions to guide customers to design probes that could generate a flap that is not complementary to the target nucleic acid.) Defendant mixed these probes with target nucleic

acid and primers. In one experiment, defendant introduced a *Taq* polymerase to this mixture; in another, it introduced a *Pfu* polymerase; and in a third, it added both a *Pfu* polymerase and a FEN-1 nuclease. The *Taq* mixture generated cleavage products 29-30 nucleotides in length, the *Pfu* mixture did not generate any detectable cleavage products, and the *Pfu* and FEN-1 combination generated cleavage products 29-30 nucleotides in length. As noted above, unlike the *Pfu* polymerase, *Taq* polymerase exhibits 5' to 3' nuclease activity.

After conducting the experiments, defendant's expert drew several conclusions from these results. He noted that the *Pfu* polymerase alone could not cleave the probe. With respect to the *Taq* polymerase mixture, he concluded that "*Taq* can cleave a non-complementary flap structure without the need to significantly displace the complementary, annealed portion of the probe molecule." As for the *Pfu* polymerase and FEN-1 combination, defendant's expert asserts that "[g]iven the nearly identical cleavage product sizes generated by FullVelocity™ and the *Taq* polymerase . . . the number of bases the *Taq* polymerase displaces before it cleaves a probe segment is similar, if not the same, as the number of bases displaced by the complex formed by the *Pfu* mutant polymerase and FEN-1, used by [defendant]." Plaintiff's expert reviewed the experiment protocol and results and concluded that it shows that the claimed cleavage structures are formed when the FullVelocity™ products are used as directed because *Pfu* FEN-1 is very specific and will efficiently cleave only particular structures. Although *Pfu* FEN-1 will cleave non-preferred

structures, plaintiff's expert asserts that the cleavage of non-preferred structures occurs so slowly that the short temperature cycling directed in the FullVelocity™ manuals will not allow for a detectable level of cleavage.

OPINION

Infringement analysis is a two-step process. First, courts construe the claims at issue and that they compare the properly construed claims to the accused device. Cybor Corp. v. FAAS Technologies, Inc., 138 F.3d 1448, 1454 (Fed. Cir. 1998) (en banc); Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996); Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996). A device infringes a patent claim if it contains every limitation set forth in that claim, either literally or by equivalence. Johnson Worldwide Assocs. v. Zebco Corp., 175 F.3d 985, 988 (Fed. Cir. 1999). "A patent is infringed if any claim is infringed." Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1220 (Fed. Cir. 1995). Claim construction is a legal determination to be made by the court while infringement is a question of fact. Vitronics, 90 F.3d at 1582; Instituform Techs., Inc. v. Cat Contracting, Inc., 161 F.3d 688, 692 (Fed. Cir. 1998).

This opinion is limited to the issue of infringement. Defendant has proposed extensive facts regarding the prosecution history of both the '543 patent and the '314 patent

that might have been made in conjunction with either a defense of patent invalidity for obviousness or of fraudulent procurement. However, defendant does not argue invalidity or fraudulent procurement, but instead uses the prosecution history in its arguments related to claim construction. “It is beyond cavil that a district court does not have authority to invalidate a patent at its own initiative if validity is not challenged by a party.” Lannom Manufacturing Co., Inc. v. U.S. Intern. Trade Commission, 799 F.2d 1572, 1579 (Fed. Cir. 1986); see also 35 U.S.C. § 282 (once patents are issued by United States Patent and Trademark Office, they are presumed to be valid; burden of establishing invalidity rests on party asserting it); Seiko Epson Corp. v. Nu-Kote International, Inc., 190 F.3d 1360, 1367 (Fed. Cir. 1999) (“A ruling of inequitable conduct in the PTO must be supported by clear and convincing evidence of material misrepresentation, made with the intent to deceive or mislead the patent examiner.”).

Although defendant did not develop an invalidity argument on summary judgment, it appears that it intends to pursue this theory in the future. In a rebuttal expert report, defendant’s expert Joseph O. Falkinham III offers the opinion that the patents are invalid in light of prior art. Plaintiff has moved to strike these portions of the expert report. Because the issue of invalidity is not relevant to the motion at hand, I will leave the motion to strike for the magistrate judge to resolve before trial.

A. Rules Governing Infringement Analysis

1. Claim construction

“[I]n interpreting an asserted claim, [a] court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history.” Vitronics, 90 F.3d at 1582. Construction of the disputed terms begins with the claim language, which serves to delineate the virtual metes and bounds of the invention, letting competitors know what they can and cannot do in the way of making and selling similar products. Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 619 (Fed. Cir. 1995) (citing Yale Lock Manufacturing Co. v. Greenleaf, 117 U.S. 554, 559 (1886)). Thus, claim construction must adhere carefully to the precise language of the claims that the patent officer has allowed. Autogiro Co. of America v. United States, 384 F.2d 391, 396 (Ct. Cl. 1967) (“Courts can neither broaden nor narrow the claims to give the patentee something different than what he set forth [in the claim].”).

In construing the language of the claims, “[t]here is a ‘heavy presumption’ that the terms used in claims ‘mean what they say and have the ordinary meaning that would be attributed to those words by persons skilled in the relevant art.’” SuperGuide Corp. v. DirecTV Enterprises, Inc., 358 F.3d 870, 874-75 (Fed. Cir. 2004) (quoting Texas Digital Systems, Inc. v. Telegenix, Inc., 308 F.3d 1193, 1202 (Fed. Cir. 2002)). Dictionaries,

encyclopedias and treatises may be used in determining the ordinary and customary meaning of claim term language, so long as the definition does not contradict any definition found in the patent documents or ascertained from them. Phillips v. AWH Corp., ___ F.3d ___, 2005 WL 1620331 (Fed. Cir. July, 12, 2005). “[U]nless compelled to do otherwise, a court will give a claim term the full range of its ordinary meaning.” Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342 (Fed. Cir. 2001).

“If the disputed claim term ‘is a term with no previous meaning to those of ordinary skill in the prior art, its meaning, then, must be found elsewhere in the patent.’” Novartis Pharmaceuticals Corp. v. Abbott Laboratories, 375 F.3d 1328, 1334 (Fed. Cir. 2004) (quoting J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 1006 F.3d 1563, 1568 (Fed. Cir. 1997)). In most instances, the specification “is the single best guide to the meaning of a disputed term.” Vitronics, 90 F.3d at 1582. Although the patent specification may not be used to rewrite the claim language, SuperGuide, 358 F.3d at 875, the specification may be used to interpret what the patent holder meant by a word or phrase in the claim, E. I. Du Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1433 (Fed. Cir. 1988).

After considering the claim language and the specification, a court may consider the final piece of intrinsic evidence: the patent's prosecution history. Vitronics, 90 F.3d at 1582. “[S]tatements made during the prosecution of a patent may affect the scope of the invention.” Rexnord, 274 F.3d at 1343. This is especially true if a particular interpretation

of the claim was considered and specifically disclaimed during the prosecution of the patent. Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co., 520 U.S. 17, 30 (1997); Vitronics, 90 F.3d at 1582-83. Generally, analysis of the intrinsic evidence will eliminate any ambiguity in the claim terms, rendering unnecessary any reference to extrinsic evidence. Vitronics, 90 F.3d at 1583.

2. Infringement

Infringement analysis requires a comparison of the properly construed claims with the allegedly infringing device or method to determine “whether all of the claim limitations are present, either literally or by a substantial equivalent, in the accused device.” Johnson Worldwide Associates, Inc. v. Zebco Corp., 175 F.3d 985, 988 (Fed. Cir. 1999). “Literal infringement of a claim exists when each of the claim limitations ‘reads on,’ or in other words is found in, the accused device.” Allen Engineering Corp. v. Bartell Industries, Inc., 299 F.3d 1336, 1345 (Fed Cir. 2002). Under the doctrine of equivalents, “a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is ‘equivalence’ between the elements of the accused product or process and the claimed elements of the patented invention.” Warner-Jenkinson Co. v. Hilton Davis Chemicals Co., 520 U.S. 17, 21 (1997). Although infringement is a question of fact, IMS Technology, Inc. v. Haas Automation, Inc., 206 F.3d 1422, 1429 (Fed. Cir. 2000), summary

judgment is appropriate where there are no material facts in dispute. Johnson Worldwide, 175 F.3d at 988.

B. Infringement by the FullVelocity™ Products

1. Direct infringement, contributory infringement and active inducement

Before getting mired down in the intricacies of the claim requirements, I will address the parties' dispute about defendant's potential liability for any infringement of the method claims at issue that might have been performed with the FullVelocity™ products. It is my understanding that plaintiff is pursuing its claims for direct infringement, contributory infringement and active inducement of infringement. See 35 U.S.C. § 271. Because "[l]iability for either active inducement of infringement or for contributory infringement is dependent upon the existence of direct infringement," Joy Technologies, Inc. v. Flakt, Inc., 6 F.3d 770, 774 (Fed. Cir. 1993) (citing cases), it is necessary to start by determining whether a jury could find defendant liable for direct infringement.

Direct infringement of a method or process claim occurs only when the process is performed and only by the entity performing the process. Id. at 774-75. "[A] method claim is not directly infringed by the sale of an apparatus even though it is capable of performing only the patented method." Id. at 775. Although defendant concedes that it has used the FullVelocity™ products as directed, it contends that its use falls under either the

experimental use exception or under the exemption in 35 U.S.C. § 271(e)(1), which applies solely for uses reasonably related to developing and submitting information used for federal regulations. Specifically, defendant asserts that it is testing the FullVelocity™ products in order to obtain approval from the Federal Food and Drug Administration.

Although defendant's testing of its products might seem to fall under the experimental use exception, the Court of Appeals for the Federal Circuit has held that the scope of the exception is markedly narrow and that a defendant bears the burden of proving its applicability. Madey v. Duke University, 307 F.3d 1351, 1361 (Fed. Cir. 2002). To qualify for the exception, a defendant's actions must be performed "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." Embrex, Inc. v. Service Engineering Corp., 216 F.3d 1343, 1349 (Fed. Cir. 2000) (quoting Roche Products, Inc. v. Bolar Pharm. Co., 733 F.2d 858, 863 (Fed. Cir. 1984)). Actions do not qualify for the experimental use defense when undertaken in the "guise of scientific inquiry" if there are "definite, cognizable, and not insubstantial commercial purposes" motivating them. Id. None of defendant's evidence shows that its actions fall into the realm of idle curiosity. To the contrary, defendant's assertion that it intends to obtain FDA approval in order to market its diagnostic assays belies any notion that its actions were without commercial motivation.

Defendant has similarly not supported its assertion that its actions are exempted under § 271(e)(1), which provides:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

In a recently decided case, the United States Supreme Court held that § 271(e)(1) might apply to experimentation that is not ultimately the subject of an FDA submission. Merck KGaA v. Integra Lifesciences I, Ltd., 125 S. Ct. 2372, 2382 (2005). (Although Merck was decided after briefing in this case was completed, both parties conscientiously alerted the court to its presence and explained what effect they thought it had to the present case.) However, the Court also confirmed that there are some bounds to the “reasonably related” standard. Id.

The exact scope of the “reasonably related” standard is not particularly relevant in this case in light of the fact that defendant has not actually said that its testing was related to obtaining FDA approval in any way. Instead, defendant relies on carefully crafted conjecture. In its proposed finding of fact, defendant asserts that it cannot market diagnostic assays without FDA approval. Dft.’s Br., dkt. #48, at 27. This assertion consists only of a bare legal conclusion that commercially marketed diagnostic assays require FDA approval; it explains nothing about defendant’s actions. Conspicuously missing from both defendant’s brief and its proposed findings of fact is a simple, straightforward assertion that its past testing of the FullVelocity™ products actually *was* performed in order to develop or

submit information to the Food and Drug Administration.

Although defendant did not mention it in either its briefs or fact proposals, plaintiff acknowledges that defendant's chief executive officer averred that defendant's testing of its own products "is driven, in part by its desire to eventually expand the utility of its FullVelocity™ products and submit products using the FullVelocity™ platform for FDA approval." Oparil Dec., dkt. #51, Exh. 2, Sorge Dec. ¶ 29. However, in a deposition taken less than two months ago, this same individual conceded that defendant was only in the "start-up phase" of pursuing the diagnostics market for its FullVelocity™ products. Ahn Dec., dkt. #56, Exh. 3, Sorge June 1, 2005 Dep. at 29:7-18.

In any event, I am not convinced that a remote desire to obtain FDA approval for products "using the FullVelocity™ platform" is sufficient to satisfy the "reasonably related" standard. Defendant's construction of § 271(e)(1) would read the term "reasonably" out of the provision, granting immunity to any testing no matter how remotely related to a hypothetical submission to a federal agency. Moreover, § 271 provides exemption "*solely* for uses reasonably related to the development and submission of information" to federal regulatory agencies; defendant's CEO testified that its testing was motivated "in part" by a desire to obtain FDA approval. Defendant will need evidence showing a far more concrete relationship between its past testing and its future intent to seek FDA approval if it intends to revive its argument under § 271(e)(1) at trial. At this point, its evidence is insufficient

to support such an argument.

If plaintiff can prove direct infringement, it may be able to hold defendant liable for inducement pursuant to 35 U.S.C. § 271(b) or contributory infringement under 35 U.S.C. § 271(c). As for inducement liability, “a person infringes by actively and knowingly aiding and abetting another’s direct infringement.” Water Technologies Corp. v. Calco, Ltd., 850 F.2d 660, 668 (Fed. Cir. 1988); see also 35 U.S.C. § 271(b). In its argument in opposition to a finding of inducement liability, defendant vacillates between asserting that the FullVelocity™ products *cannot* be used in a way that infringes either the ‘543 patent or the ‘314 patent and that infringement will not occur when the FullVelocity™ products are used *as directed*. Because an entity cannot be held liable for infringement it did not actively promote, it is largely irrelevant whether the FullVelocity™ products *can* be used to infringe the claims. See, e.g., ICN Pharmaceuticals, Inc. v. Geneva Pharmaceuticals Technology Corp., 272 F. Supp. 2d 1028, 1049 (C.D. Cal. 2003) (potential off-label uses could not be basis for inducement liability where there was no evidence defendant encouraged or promoted off-label use). Furthermore, the parties have stipulated that “the materials for performing reactions with the accused FullVelocity™ products . . . had no substantial use other than the use set forth in the instruction manuals and product inserts which accompany those products.” Oparil Dec., dkt. #51, Ex. 55, ¶ 3. Thus, I will focus the analysis on whether the FullVelocity™ products cause infringement when used as directed. (Although

defendant emphasizes its offer to change its instruction manuals so that its customers would be directed to use only probes with *non*complementary 5' flaps, its reliance on this change is misplaced. At most, such an alteration would be relevant only to the availability of future injunctive relief.)

As for contributory infringement, 35 U.S.C. § 271(c) provides that “[w]hoever offers to sell or sells within the United States . . . a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.” In opposition to plaintiff’s claim of contributory infringement, defendant asserts that “the buffers and enzymes of the accused products are suitable for substantial noninfringing use, as evidenced by the fact that the enzymes and their buffers are sold by a number of companies.” Dft.’s Br., dkt. #48, at 41. Defendant will not be able to evade liability under § 271(c) so easily. First, as I have just noted, defendant has stipulated to the exact opposite: that “the materials for performing reactions with the accused FullVelocity™ products . . . had no substantial use other than the use set forth in the instruction manuals and product inserts which accompany those products.” Oparil Dec., dkt. #51, Exh. 55, ¶ 3. Moreover, defendant’s suggestion that the FullVelocity™ enzymes are sold by a number of other companies conflicts with the emphasis

defendant places elsewhere on the fact that the polymerase enzyme sold with the FullVelocity™ products is a mutant variant of naturally occurring *Pfu* polymerases. E.g., Dft.'s Resp. to Plt's PFOF, dkt. #50, ¶¶ 289-92. Defendant will be held to its stipulated fact. Thus, if I find that use of the FullVelocity™ products as directed results in infringement of either the '543 patent or the '314 patent, defendant may be held liable under § 271(c) as well as § 271(b).

2. Effect of EraGen Biosciences holding

In support of its motion for summary judgment, plaintiff invokes the claim constructions made in Third Wave Technologies, Inc. v. EraGen Biosciences, Inc., 02-C-507-C, 2003 WL 23100277, *10 (W.D. Wis. Mar. 18, 2003). Defendant contends that these conclusions are not binding on it. Defendant is correct; a second alleged infringer is not bound by prior claim construction unless it had a full and fair opportunity to litigate the construction in the first infringement action. Jackson Jordan, Inc. v. Plasser American Corp., 747 F.2d 1567, 1574-75 (Fed. Cir. 1984); see generally Blonder-Tongue Laboratories, Inc. v. University of Illinois Foundation, 402 U.S. 313, 329 (1971). However, defendant has not taken advantage of the opportunity it had in responding to plaintiff's motion to provide any reason why it believes the claim construction in EraGen is wrong. Having had a full and fair opportunity to litigate the EraGen claim construction issues, defendant's due process

rights will not be infringed by the adoption of the construction set out in that case. Parklane Hosiery Co., Inc. v. Shore, 439 U.S. 322, 327 n.7 (1979) (“It is a violation of due process for a judgment to be binding on a litigant who was not a party or a privy and therefore has never had an opportunity to be heard.”).

Because defendant has not provided any reason to believe that I would reach different conclusions were I to revisit the relevant issues, I find that the reagents may be provided before or during the mixing step; that the term “complementary” refers to “bases that are related by the base pairing rules” that are not limited to bases that hydrogen bond in a standard “Watson-Crick” fashion; and that the term “non-target cleavage products” means products of a cleavage reaction that are derived from the 5' portion of the first oligonucleotide. Markman, 517 U.S. at 391 (even though issue preclusion cannot be asserted against new defendant, “treating interpretive issues as purely legal will promote (though it will not guarantee) intrajurisdictional certainty through the application of stare decisis on those questions not yet subject to interjurisdictional uniformity under the authority of the single appeals court”).

Defendant does raise one argument related to the opinion in EraGen that I hesitate to address because of its frivolity. Defendant contends that both patents in suit distinguish the prior art by asserting that the claimed subject matter amplifies the signal molecule rather than the target nucleic acid and that although I held in EraGen that the oligonucleotides can

be amplified by any means, I “made it clear” that the target was not amplified. The easiest way to address this argument is to quote the passage from EraGen to which defendant refers:

It is true that plaintiff's patents distinguish the inventions from polymerase chain reaction. However, the patents do not differentiate between methods of creating oligonucleotides inside or outside the mix, before or during the mixing step. **The distinction plaintiff makes in the patents between PCR and its inventions is in the method of *detecting* sequences, *not* in the method of providing the ingredients necessary to perform the detection.** See Pat. '543, cols. 1-5; Pat. '314, cols. 1-5 (describing PCR as one method "to detect and characterize specific nucleic acid sequences and sequence variations"); see also Pat. '543, col. 26, lines 16-19; Pat. '314, col. 23, lines 11-14 ("This method relies upon the amplification of the detection molecule rather than upon amplification of the target sequence itself as do existing methods of detecting specific target sequences.")

The distinction I drew was between using amplification as a means of providing the reagents and as a means of detecting the presence of a particular target nucleic acid. It was not, as defendant suggests, between using PCR as a means of providing oligonucleotides and as a means of providing target nucleic acid. When the FullVelocity™ products are used as directed, detection is accomplished by the observation of fluorescence from the probe, not by the observation of amplification of the target nucleic acid.

3. Cleavage agent/means

The '314 patent claims a method requiring the provision of a “cleavage agent” and the '543 patent claims a method requiring the provision of a “cleavage means.” Both patents define a cleavage means as “refer[ring] to any means which is capable of cleaving a cleavage

structure, including but not limited to enzymes.” ‘543 Pat., col. 20, lns. 55-57; ‘314 Pat., col. 18, lns. 6-8. Further, the specifications state that “[t]he cleavage means of the invention cleave a nucleic acid molecule in response to the formation of cleavage structures; it is not necessary that the cleavage means cleave the cleavage structure at any particular location within the cleavage structure.” ‘543 Pat., col. 21, lns. 2-7; ‘314 Pat., col. 18, lns. 20-25. “Native DNAPs having 5' nuclease activity (e.g., *Taq* DNA polymerase, *E. coli* DNA polymerase I) and, more specifically, modified DNAPs having 5' nuclease but lacking synthetic activity” are identified as potential cleavage means. ‘543 Pat., col. 20, lns. 58-61; ‘314 Pat., col. 18, lns. 9-12. (The specification for the ‘314 patent does not define “cleavage agent.”)

Plaintiff identifies *Pfu* FEN-1 as the claimed “cleavage agent/means.” It is undisputed that *Pfu* FEN-1 is a thermostable structure-specific 5' nuclease capable of cleaving the cleavage structures identified in the ‘314 patent and claim 16 of the ‘543 patent. Defendant raises two unpersuasive arguments in its attempt to show that plaintiff has not shown that the cleavage agent/means element has been satisfied. First, defendant asserts that “cleavage means” is a means-plus-function limitation and that as such, it is limited to those cleavage means disclosed in the patent specification pursuant to 35 U.S.C. § 112. Dft.’s Resp. to Plt.’s PFOF, dkt. #50, ¶¶ 80, 102 and 116. An initial problem with this argument is that it misrepresents § 112, which provides that means-plus-function limitations are to be

construed to cover both “the corresponding structure, material, or acts described in the specification *and equivalents thereof*.” Furthermore, the patent anticipates the use of FEN-1 nucleases as cleavage agent/means. In the summary of the invention section of the specification, the patents identify “[t]hermostable structure-specific nucleases from the FEN-1, RAD2 and XPG class of nucleases” as preferred types of nucleases. ‘543 Pat., col. 6, lns. 62-64; ‘314 Pat., col. 6, lns. 63-65. *Pfu* FEN-1 is a thermostable structure-specific FEN-1 nuclease.

Defendant’s second argument is little more than an erroneous conflation of claim requirements. Defendant contends that although *Pfu* FEN-1 is a thermostable 5' nuclease, it does not cleave a “cleavage structure” when used as instructed in the FullVelocity™ manuals because a “cleavage structure” never forms. E.g., Dft.’s Resp. to Plt.’s PFOF, dkt.# 50, ¶¶ 132, 134. If this is true, the claim for infringement will fail for lack of a “cleavage structure” and not for lack of a cleavage means. The patentees chose to be their own lexicographers and were clear in defining a cleavage means as “any means which is *capable* of cleaving a cleavage structure, including but not limited to enzymes.” ‘543 Pat., col. 20, lns. 55-57; ‘314 Pat., col. 18, lns. 6-8 (emphasis added). Thus, a cleavage means/agent is provided whether or not it actually comes into contact with a cleavage structure. Because it is undisputed that *Pfu* FEN-1 is *capable* of cleaving the claimed cleavage structure, plaintiff has satisfied its burden of showing that a “cleavage means” or “cleavage agent” is provided

when the FullVelocity™ products are used as directed.

4. Source of target nucleic acid

Next, both methods claimed in the '543 patent and the '314 patent require the provision of a source of target nucleic acid. Defendant's product manuals instruct users to provide experimental gDNA, cDNA, plasmid DNA or RNA, any of which provide a potential source of target nucleic acid. The '543 patent claims a target nucleic acid having a first, second and third region with the first region downstream of the second region and the second region downstream from and contiguous to the third region. The '314 patent claims a target nucleic acid having two regions, the second region being downstream from and contiguous to the first region.

Defendant contends that one of ordinary skill in the art would not be able to identify a particular region at the target or portion of the oligonucleotide to practice the invention or know when she is practicing the invention because "[t]he patent only describes 'regions' in terms of their location relative to each other, and their ability to base pair with 'portions' of oligonucleotides, where the 'portions' are circularly defined in terms of their ability to bind (*i.e.*, their functionality) the 'regions.'" Deft.'s Resp. to Plt.'s PFOF, dkt. #50, ¶ 82. (Of course, a person of ordinary skill would know that the target nucleic acid has the claimed regions *after* the method is performed by virtue of the production of non-target cleavage

products, so I must assume that defendant means that a person does not know *before* mixing whether she might infringe either patent.) Defendant does not indicate what practical effect it believes this observation has to this case, that is, whether this asserted lack of clarity renders the patent invalid for indefiniteness, 35 U.S.C. § 112, whether it suggests a particular claim interpretation should be adopted or whether it means there can be no infringement. As noted above, the defense of patent invalidity must be clearly raised. As for the possibility that defendant's argument might have some bearing on claim construction, defendant does not propose any definition of the term "regions" that this supposed circularity would support.

This leaves the possibility that defendant is suggesting that the asserted lack of clarity has some bearing on the issue of infringement. Defendant argues that a person of ordinary skill in the art would not know when she is practicing the invention. However, intent is not an element of direct infringement. Hilton Davis Chemical Co. v. Warner-Jenkinson Co., Inc., 62 F.3d 1512, 1519 (Fed. Cir. 1995), rev'd on other grounds, 520 U.S. 17, 35, (1997) (citing Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 478 (1974)); but see Hoechst Celanese Corp. v. BP Chemicals Ltd., 78 F.3d 1575, 1583 (Fed. Cir. 1996) (intent to infringe may justify enhanced damages).

Although knowledge and intent are relevant to inducement liability, Hewlett-Packard Co. v. Basch & Lomb, Inc., 909 F.2d 1464, 1469 (Fed. Cir. 1990), undoubtedly defendant

intends that its products confirm the presence of particular sequences at least some of the time they are used. That one skilled in the art would not know in advance whether she is about to infringe is simply a result of the fact that the claims were drafted in such a way that infringement occurs only when the sample DNA actually contains the particular target nucleic acid sequence to be detected. Perhaps this is less than artful drafting, but it is not particularly confusing. If defendant's products infringe either of the patents when used as directed with a target nucleic acid containing the particular sequence to be detected, then defendant knows that the sale of its products will result in infringement at least some of the time. Furthermore, two of defendant's customers have already detected the presence of specific target nucleic acid sequences using the FullVelocity™ products. Defendant cannot claim that it did not know or expect that the FullVelocity™ products would work.

Because defendant instructs its users to provide experimental gDNA, cDNA, plasmid DNA or RNA, some of which will have the first, second and third regions defined in the patents, plaintiff has satisfied its burden of showing that a "source of target nucleic acid" is provided when the FullVelocity™ products are used as directed.

5. First and second oligonucleotides have 3' and 5' portions

Both patents claim a first and second oligonucleotides having certain portions. In the '543 patent, both oligonucleotides have a 3' portion and a 5' portion. In the '314 patent,

the first oligonucleotide has a portion “completely complementary to said first portion of said first target nucleic acid” and the second oligonucleotide has a 3' portion and a 5' portion. In support of its motion, plaintiff points out that defendant directs its customers to provide a probe and a primer; plaintiff identifies these as the first and second oligonucleotides respectively. Defendant marshals three arguments contesting plaintiff's showing that the first and second oligonucleotides are provided when the FullVelocity™ products are used as directed. All three are red herrings.

First, defendant contends that the probes and primers it instructs its users to provide do not qualify as “oligonucleotides” because the specifications limit oligonucleotides to 30 nucleotides or less. To the contrary, the specifications define the term “oligonucleotide” as “a molecule comprised of two or more deoxyribonucleotides or ribonucleotides, preferably at least 5 nucleotides, more preferably at least about 10-15 nucleotides and more preferably at least about 15 to 30 nucleotides. The exact size will depend on many factors, which in turn depends on the ultimate function or use of the oligonucleotide.” ‘543 Pat., col.18, lns. 58-6; ‘314 Pat., col. 16, lns. 10-14. Instead of placing a cap on the number of nucleotides an oligonucleotide can have, the patent specifications indicate a preference for longer strands. Although defendant is correct that “oligonucleotide” literally means a few nucleotides, a single DNA molecule is made up of thousands of nucleotides. In this context, what constitutes a few may be far more than 30. See, e.g., Haijuan Yang *et al.*, *The BRCA2*

homologue BRH2 nucleates RAD51 filament formation at a dsDNA-ssDNA junction, 433 NATURE 653, 656 (Feb. 2005) (using 80-nucleotide-long “oligonucleotide”); Youming Zhang *et al.*, *Phage annealing proteins promote oligonucleotide-directed mutagenesis in Escherichia coli and mouse ES cells*, 4 BMC Molecular Biology 1, 5 (using oligonucleotides ranging from 16-160 nucleotides in length); Xin Bai *et al.*, *Quantitative polymerase chain reaction for human herpes virus diagnosis and measurement of Epstein–Barr virus burden in posttransplant lymphoproliferative disorder*, 43 Chemical Chemistry 1843, 1844 (1997) (using oligonucleotide 100 nucleotides in length). In fact, a 119-nucleotide-long “oligonucleotide” was used in one of the studies that defendant cites in support of some of its proposed findings of fact. Martin A. Greagg *et al.*, *A read-ahead function in archaeal DNA polymerases detects promutagenic template-strand uracil*, 96 PROCEEDINGS NATIONAL ACADEMY SCIENCES 9045 (Aug. 1999).

Defendant’s second argument is that the term “portions” is ambiguous. Its argument is simply the inverse of its argument that the term “regions” is ambiguous, namely that “portions” and “regions” are circularly defined by their relationship to one another. When dealing with a process to identify an unknown, one skilled in the art should not find it surprising, let alone confusing, that she cannot determine the presence of that unknown until after the reaction is complete. This does not mean that one skilled in the art cannot understand what is being taught in the patent. A patent need only be specific enough that those skilled in the art would understand what is claimed when the claim is read in light of

the specification. Morton International, Inc. v. Cardinal Chemical Co., 5 F.3d 1464, 1470 (Fed. Cir. 1993).

Finally, defendant contends that the reference to “said first portion of said first target nucleic acid” is ambiguous because it lacks an antecedent. For the sake of simplicity, I will repeat the relevant passages here with the pertinent language highlighted:

ii) a source of target nucleic acid, said target nucleic acid comprising **a first region** and a second region, said second region downstream of and contiguous to said first region;

iii) a first oligonucleotide, wherein at least a portion of said first oligonucleotide is completely complementary to **said first portion of said first target nucleic acid**;

Defendant’s argument imposes an undue standard of technical precision on the patent claims. When read in context, it is obvious even to one not skilled in the art that “said first portion of said first target nucleic acid” refers to the “first region” of the source of target nucleic acid described in subsection (ii).

6. Mixing

Of slightly more substance is the parties’ debate whether “mixing” includes the process of subjecting the combined reagents to a series of temperature cycles as instructed by the FullVelocity™ manuals. According to defendant, a second oligonucleotide is not “provided” using the FullVelocity™ products until after mixing is complete. (I held in

EraGen that the reagents may be provided either before or during mixing but not after.) As I understand it, defendant reasons that a second oligonucleotide must have a 3' portion that is completely complementary to the second region of the target nucleic acid; the primer used with the FullVelocity™ products does not develop a 3' portion that is completely complementary to a second region of a target nucleic acid until it is extended by the mutant *Pfu* polymerase via a polymerase chain reaction; the polymerase chain reaction cannot occur until after the 5' end of the primer anneals to the target nucleic acid; the 5' end of the primer cannot anneal to the target nucleic acid until after the target undergoes denaturation (the DNA and RNA supplied by defendant's customers are double-stranded when initially added to the mixture); denaturation will not occur until the mixture is heated to 95°C; and finally, the mixture is not heated to 95°C until after mixing is complete. Plaintiff attacks the final step in defendant's chain of reasoning, contending that defendant wrongly assumes that "mixing" does not include placing the reagent mixture into a thermocycler and subjecting it to prescribed temperature cycles.

Plaintiff proposed as fact that "[o]ne of ordinary skill in the art reading claim 16 would have understood the requirement that mixing occur under appropriate reaction conditions to allow the claimed reagents to form a cleavage structure." Plt.'s PFOF, dkt. #32, at ¶ 192. Although defendant purported to dispute this proposal, its proposed responsive fact is identical to plaintiff's proposed finding of fact, as is the expert testimony

that defendant cited. Dft.'s Resp. to Plt.'s PFOF, dkt. #50, at ¶ 192 (citing Oparil Dec., Exh. 11, Falkinham Dec. at ¶ 133). Pursuant to this court's summary judgment rules, I have treated plaintiff's proposed finding of fact as undisputed. Even if I were to assume that defendant had not intended to concede this point and that its error was merely a typographical one, plaintiff's proposal is a natural extension of the claim language, which in both patents provides for "mixing [the reagents] to create a reaction mixture *under reaction conditions such that*" portions of the oligonucleotides anneal to the target nucleic acid. '543 Pat., col. 285, lns. 12-15; '314 Pat., col. 177, lns. 60-64. A fair reading of this language is that "mixing" includes those conditions necessary for the oligonucleotides to anneal to the target nucleic acid, in this case, subjecting the mixture to the temperature cycles.

7. Annealing

Plaintiff contends that the term "annealed" means "the pairing, or hybridization, of complementary nucleic acid molecules via hydrogen bonding to form a duplex, or double-stranded base pair or base paired region of nucleic acid." Plt.'s PFOF, dkt. #32, ¶ 126. Defendant tries to put this proposed finding into dispute by arguing that "[a]nnealing is not the same thing as hybridizing, especially in the context of an extended primer. One of ordinary skill in the art understands that when you extend a primer, it does not "hybridize" because hybridization is the finding of one of [sic] sequence by another." Dft.'s Resp. to

Plt.'s PFOF, dkt. #50, ¶ 126. Contrary to defendant's assertion in litigating this case, its instruction manuals provide that "[d]uring the combined annealing-extension step of PCR, the primers and the probe hybridize with the target." Oparil Dec., dkt. #51, exhs. 23 and 24. According to defendant's own description of its process, annealing and hybridization are synonymous and primer extension and annealing are co-extensive.

Furthermore, the claim language calls exclusively for the annealing of the first and second oligonucleotides to the target; to the extent that hybridization has an additional "finding" component, the claims at issue do not contain this limitation. It is undisputed that "annealing" means at least "the pairing . . . of complementary nucleic acid molecules via hydrogen bonding to form a duplex, or double-stranded base pair or base paired region of nucleic acid." In polymerase chain reactions, the extended primer "anneals" to the target. JONATHAN P. CLEWLEY, THE POLYMERASE CHAIN REACTION FOR HUMAN VIRAL DIAGNOSIS, 4 (CRC Press 1995) (every PCR cycle requires re-denaturation); MAXIM D. FRANK, UNRAVELING DNA, 132-133 (Addison-Wesley 1993) (same). Thus, I conclude that both the probe and the primer anneal to the target when the FullVelocity™ products are used as directed.

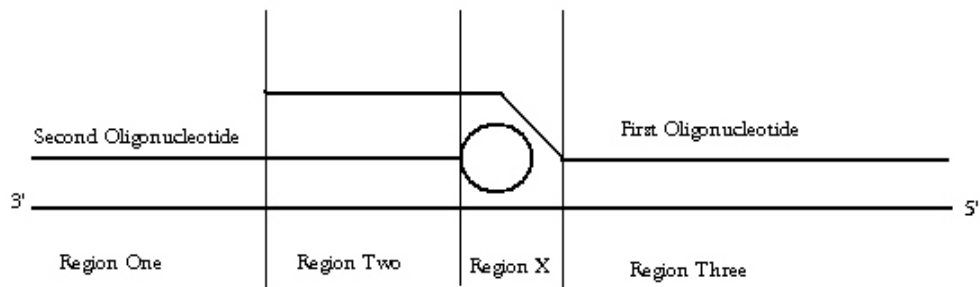
8. Region contiguity

Tangentially related to the question of annealing is whether the FullVelocity™

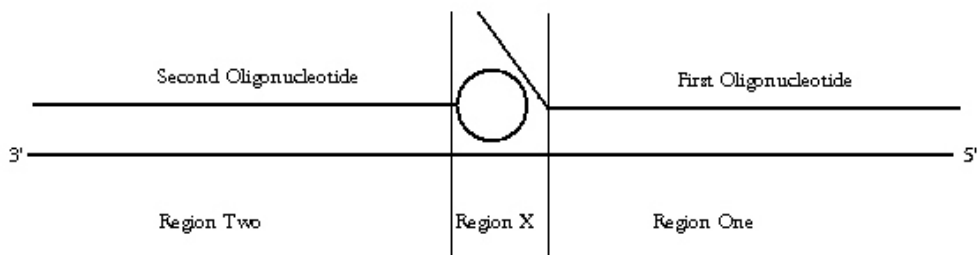
products cause the probes and extended primers used therein to anneal to the target in such a manner as to define regions that meet the claim contiguity requirements. The '314 patent requires that the first and second regions of the target nucleic acid be contiguous and the '543 patent claims contiguity between the second and third regions. In the '314 patent, the first region is that segment of the target nucleic acid in which "at least a portion of [the] first oligonucleotide is completely complementary" and to which that completely complementary portion anneals as a result of the reaction conditions of the mixing step. The second region is that segment of the target in which the 5' portion of the second oligonucleotide is completely complementary and to which that portion anneals as a result of the reaction conditions of the mixing step. In the '543 patent, the second region is defined as that in which the 5' portion of the first oligonucleotide and the 3' portion of the second oligonucleotide "each contain [a] sequence [that is] fully complementary." The third region is that portion of the target nucleic acid in which the 5' portion of the second oligonucleotide "contains [a] sequence [that is] complementary."

Defendant contends that the physical space occupied by the polymerase prevents contiguity between regions from ever occurring. (The parties do not dispute that the term "contiguous" means that there are no nucleotides in between the relevant sections or regions.) As I understand it, defendant's argument can be visually (albeit crudely) depicted in the diagrams in illustration no. 6, with the area marked "Region X" representing the space

allegedly occupied by the polymerase. As depicted in these illustrations, the existence of a region X would destroy contiguity between regions two and three in the '543 patent and between regions one and two in the '314 patent:



'543 Patent



'314 Patent

Illustration No. 6

With respect to the '543 patent, I understand defendant to argue that if the space is occupied by the polymerase, it cannot be part of region two because the 3' portion of the second oligonucleotide would not be fully complementary to the target nucleic acid and Furthermore, this space could not be part of region three because the 3' portion of the first oligonucleotide would not be annealed to the target nucleic acid. With respect to the '314 patent, I understand defendant to argue that if the space is occupied by the polymerase, it could not be part of region two to because the 5' portion of the second oligonucleotide would be neither fully complementary nor annealed to this area on the target nucleic acid and that it would not be part of region one because the first oligonucleotide would not be annealed to this portion of the target.

As noted above, the term "contiguous" means that there are no nucleotides between the relevant sections or regions. Defendant contends that the presence of the polymerase would destroy contiguity because the space it occupies on the target nucleic acid is approximately four to six nucleotides long. To support its assertion that the mutant *Pfu* polymerase used in the FullVelocity™ products occupies approximately four to six nucleotides on the target nucleic acid, defendant cites Martin A. Greagg *et al.*, *A read-ahead function in archael DNA polymerases detects promutagenic template-strand uracil*, 96 PROCEEDINGS NATIONAL ACADEMY SCIENCES 9045 (Aug. 1999). Dft.'s PFOF, dkt. #49, ¶ 38. In the study, Greagg *et al.* describe the finding of researchers that DNA polymerases from several

hyperthermophilic archaea, including *Pfu*, are able to detect the presence of a uracil-based nucleotide in a target strand approximately four to six nucleotides ahead of the last nucleotide they added to the 3' end of the primer. The authors observe that “the spacing of 4-6 nucleotides between the last nucleotide incorporated into the primer and the position of the uracil is suggestive of a uracil-sensor ‘leading’ the polymerase activity in the archaeal enzymes.” *Id.* at 9047.

To be sure, the conclusion defendant derives from the results found in the Greagg study requires certain inferences. One is that the polymerase could not detect an upstream nucleotide without displacing all intervening annealed upstream nucleotides. Second is that the mutant *Pfu* polymerase used in the FullVelocity™ products would act in the same manner as the wild type *Pfu* polymerase used in the study. Nonetheless, these inferences are reasonable ones. Thus, I will take defendant’s conclusion as true for summary judgment purposes. Because I will assume that the mutant *Pfu* polymerase displaces any nucleotides annealed to the target approximately 4 to 6 nucleotides upstream from the most recently added nucleotide on the 3' end of a downstream primer, the question becomes whether defendant is correct that contiguity is therefore destroyed.

Plaintiff argues that it would not be destroyed, emphasizing that the ‘543 patent requires only that the oligonucleotides *contain* sequences complementary or completely complementary to the relevant regions and that the ‘314 patent requires only that the first

oligonucleotide have “at least a portion” that is completely complementary to region one and that the second oligonucleotide have a 5' portion that is completely complementary to the second region. Using depictions similar to those in Illustration No. 6, I understand plaintiff to suggest that the relevant regions in the '543 patent can be defined as depicted in either of the following:

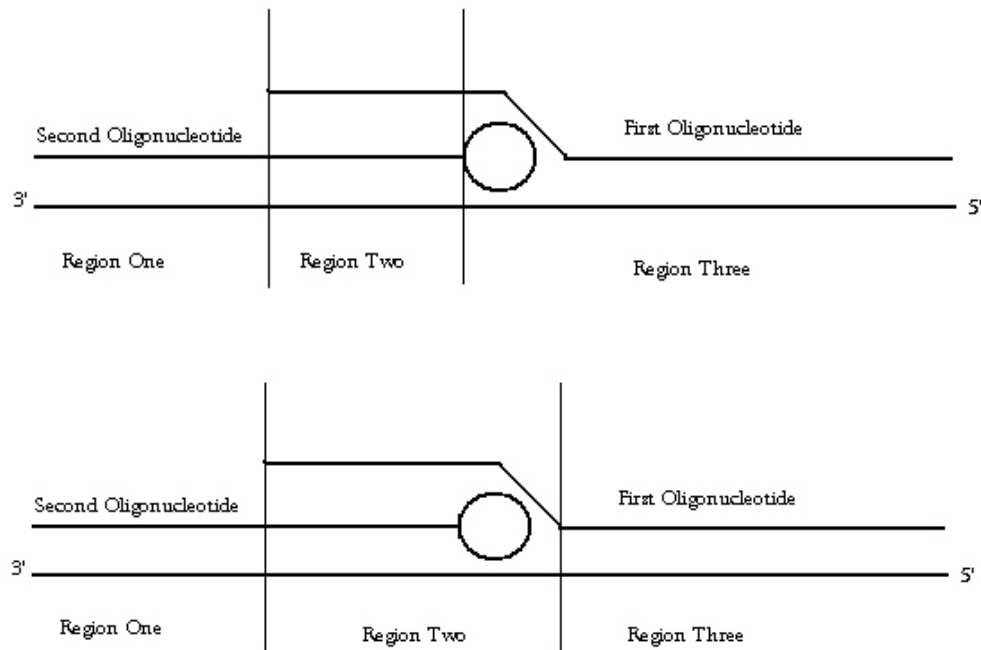


Illustration No. 7

With respect to the '314 patent, I understand plaintiff to argue that the relevant regions can be defined as depicted in either of the following:

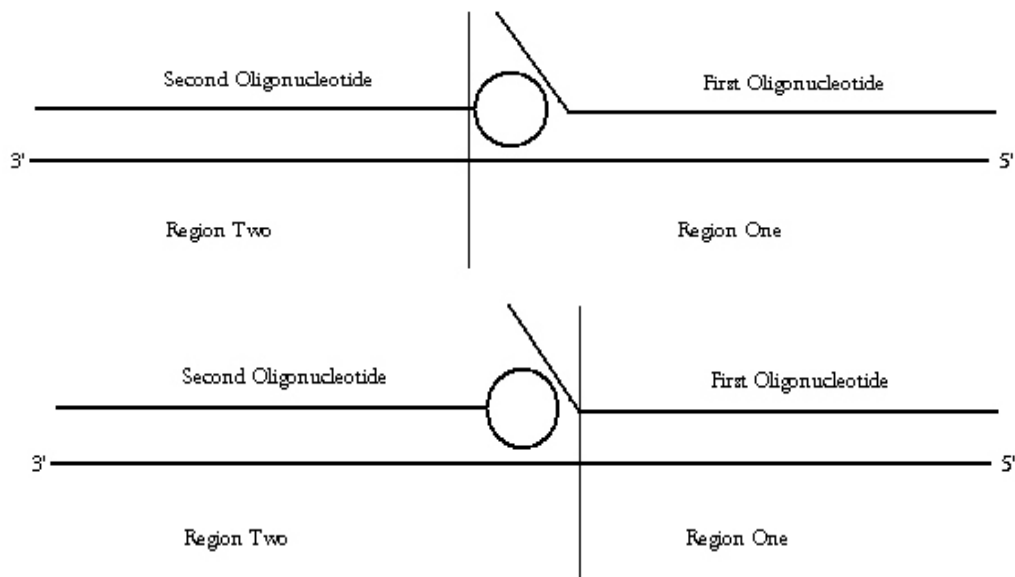


Illustration No. 8

As I understand plaintiff's argument, it is that all the limitations are met if the regions are defined as depicted above. In either depiction of the '543 patent, the second region is contiguous to and downstream of the third region, the first oligonucleotide has a 3' portion that *contains* a sequence complementary to the third region and is annealed to the third region and a 5' portion that *contains* a sequence fully complementary to the second region and the second oligonucleotide has a 3' portion that *contains* a sequence complementary to the first region and is annealed to the first region and a 5' portion that *contains* a sequence fully complementary to the second region. In either depiction of the '314 patent, the second region is downstream of and contiguous to the first region, a portion of the first

oligonucleotide is completely complementary and annealed to the first region and the 5' portion is completely complementary and annealed to the second region.

Plaintiff's argument rests on an assumption that where the claims require that portions of the oligonucleotides be complementary or annealed to certain regions, the oligonucleotides need be complementary to only a portion and not the entirety of the relevant region. An initial problem with this assumption is that it enjoys no textual support. The patents claim oligonucleotides that contain sequences that are complementary to the regions, not regions that contain sequences complementary to the oligonucleotide portions. For example, claim 16 of the '543 patent requires that "said 5' portion of said first oligonucleotide and said 3' portion of said second oligonucleotide each contain sequence fully complementary to *said second region*." (Emphasis added). Had the patentees intended to claim a cleavage structure in which these portions are fully complementary to only a *part* of "said second region" they could have said so.

Furthermore, reading the claims to require that the oligonucleotides be complementary to only portions of the regions would render the location of the region boundaries indeterminate. As shown in illustrations nos. 7 and 8, plaintiff's construction allows for multiple characterizations of the region boundaries. This leads to yet another problem: the region borders could be manipulated to meet the contiguity requirements. Moreover, there is no support for plaintiff's construction in the claim specifications. To the

contrary, the '543 patent contains a depiction of the cleavage structure claimed, illustration no. 1, in which the oligonucleotides are annealed and complementary to the entire defined regions.

Finally, plaintiff's construction is at odds with the prosecution history. As defendant emphasizes, plaintiff distinguished its claimed cleavage structure in the '543 patent from the Gelfand prior art on the basis that the Gelfand prior art did not claim a region of overlap in the regions of complementarity of the two oligonucleotides. Under plaintiff's construction, the first oligonucleotide might have a sequence fully complementary to one part of region two and the second oligonucleotide contain a sequence fully complementary to a different part of region two, leaving no overlap in the regions of complementarity. In addition, plaintiff distinguished its claimed cleavage structure from that disclosed by Lyamichev using the diagram in illustration no. 2. Plaintiff noted that regions two and three are not contiguous in the structure Lyamichev disclosed. However, if one were to adopt the construction plaintiff now advances, under which the 5' portion of the first oligonucleotide need only contain a sequence fully complementary to a part of region two, then the structure disclosed by Lyamichev in illustration no. 2 would be encompassed by claim 16 of the '543 patent. The upstream boundary of region two could simply be shifted upstream to meet the downstream border of region three.

Because plaintiff's construction is at odds with the claim language, patent

specifications and prosecution history, I find that the '543 patent requires first and second oligonucleotides having 3' and 5' portions, wherein the 3' portion of said first oligonucleotide contains a sequence complementary to the entirety of the third region of the target nucleic acid and the 5' portion of the first oligonucleotide and the 3' portion of the second oligonucleotide each contain sequence fully complementary to the entirety of the second region of said target nucleic acid, and the 5' portion of the second oligonucleotide contains a sequence complementary to the entirety of the first region of said target nucleic acid. In addition, I find that the '314 patent requires a first oligonucleotide wherein at least a portion of the first oligonucleotide is completely complementary and annealed to the entirety of the first region and a second oligonucleotide wherein the 5' portion is completely complementary and annealed to the entirety of the second region.

Thus construed, none of the depictions in illustrations nos. 7 or 8 meet the claim limitations. In the top depiction of the '543 patent, the 3' portion of the second oligonucleotide does not contain a sequence that is completely complementary to the entirety of region two. In the lower '543 diagram, the 3' portion of the second oligonucleotide, which must be annealed to the target and thus ends where the oligonucleotide becomes dissociated, does not contain a sequence that is complementary to the entirety of the third region. In the top depiction of the '314 patent, the first oligonucleotide does not contain a portion that is annealed to the entirety of region one and

in the bottom depiction, the second oligonucleotide does not contain a 5' portion that is completely complementary and annealed to the entirety of region two.

Because I find plaintiff's first theory unconvincing, I turn to its second argument, which is that the *Pfu* polymerase dissociates from the 3' end of the extended primer before cleavage. In support of its related proposed findings of fact, Plt.'s PFOF, dkt. # 32, ¶¶ 385-391, plaintiff cites the affidavit of its expert, John Tainer, who explains that *Pfu* FEN-1 must bind several base pairs on the probe and several base pairs on the primer in order to cleave DNA with non-negligible efficiency. Casimir Dec., dkt. #33, Ex. 7, ¶ 56. Accordingly, Tainer explains, *Pfu* FEN-1 cannot cleave the hydrolysis probe unless the *Pfu* polymerase dissociates from the 3' end of the extended primer. *Id.* at ¶ 61. Pursuant to this court's summary judgment rules, I accept plaintiff's proposition regarding dissociation as true unless defendant puts it in dispute.

To that end, defendant raises two arguments, neither of which is adequately supported by the citations defendant provides. First, defendant asserts that the mutant *Pfu* polymerase used in the FullVelocity™ products has high processivity, which defendant defines to mean that the polymerase will not dissociate from the structure during the extension step of a PCR cycle. Assuming this assertion were true, it would not foreclose the possibility that the mutant *Pfu* polymerase might dissociate during some other stage of the PCR cycle. In any event, the patent application that defendant cites in support of this

assertion does not go so far as defendant suggests. These applications indicate that mutant polymerases, including the V93R used in the FullVelocity™ products, may fuse with polypeptides that increase processivity to form a chimera. U.S. Patent Appl. Pub. No. 20040086890 at ¶¶ 40-41 and 52; U.S. Patent Appl. Pub. No. 20040091873 at ¶¶ 32-35. Defendant cites no evidence suggesting that the V93R used in the FullVelocity™ products forms such a chimera. Furthermore, the phrase “high processivity” does not appear in either application. Thus, even if the V93R mutant were a polypeptide chimera, this would mean only that it has an enhanced resilience to dissociation, not that it would not or could not dissociate.

Second, defendant suggests that *Pfu* FEN-1 and the *Pfu* polymerase may exist as a single complex and thus, the *Pfu* polymerase need not dissociate to effect cleavage. To support this proposition, defendant cites Rajendra Prasad *et al.*, *Fen1 Stimulation of DNA polymerase β Mediates an Excision Step in Mammalian Long Patch Base Excision Repair*, 275 The Journal of Biological Chemistry Feb. 11, 2000, at 4460, 4466. If anything, this citation suggests just the opposite. Prasad *et al.* note that although they attempted to identify interactions between pol beta polymerase and FEN-1, they were not able to demonstrate any. *Id.* at 4466 (“Using purified β -pol and FEN1, we have been unable to demonstrate an interaction between these two enzymes.”).

Although Prasad *et al.* note that other researchers had previously suggested that a

FEN-1 and β -pol from rat hepatoma cell extract might exist as a complex in cells because of their finding of co-purification, *Id.* (citing D. C. Rein, A. J. Recupero, M. Reed and R. R. Meyer, 1 THE EUKARYOTIC NUCLEUS 95-124 (1990)), this allusion is too remote to support defendant's suggestion that the archaeal *Pfu* FEN-1 and *Pfu* polymerase contained in the FullVelocity™ exist as a complex. Although it might be reasonable to assume that a mutant has the same qualities as its wild type counterpart absent evidence to the contrary, expert testimony is necessary to conclude that enzymes derived from archaea bacteria will have the same characteristics as enzymes derived from mammals. The only evidence cited by the parties on this issue is the affidavit of plaintiff's expert, who avers that the β -pol polymerase extracted from rat hepatoma cells is not biologically representative of *Pfu* polymerase. Ahn Dec., dkt. # 56, Exh. 6, Sec. Tainer Aff. ¶ 42-43. Accordingly, I find no dispute with respect to plaintiff's proposed findings of fact regarding dissociation by the *Pfu* polymerase prior to cleavage.

If the polymerase dissociates from the structure, then it is not occupying space that prevents region contiguity. However, dissociation would only remove an obstacle to contiguity. To establish contiguity, one of two things has to occur. Either the *Pfu* polymerase would have to supply additional corresponding nucleotides that join the 3' end of the extended primer to fill the gap before dissociating or the previously displaced nucleotides on the probe would have to re-anneal with the target as the obstructing

polymerase moves. Neither party has submitted any proposed findings of fact regarding either possibility. Thus, I must deny plaintiff's motion for summary judgment.

One final note as a matter of clarity. Defendant's expert reached one conclusion about the formation of the claimed cleavage structure when the FullVelocity™ products are used as directed; plaintiff's expert reached the opposite conclusion. The existence of this dispute means that plaintiff's expert testimony does not provide a sufficient basis on which to award plaintiff summary judgment. I leave it to the jury to determine whose explanation of the test results is more plausible.

ORDER

IT IS ORDERED that

1. The claims of plaintiff Third Wave Technologies, Inc.'s U.S. Patent Nos. 6,090,543 and 6,348,314 are construed as follows:
 - a. Reagents may be provided before or during the mixing step;
 - b. The term "complementary" refers to "bases that are related by the base pairing rules" that are not limited to bases that hydrogen bond in a standard "Watson-Crick" fashion;
 - c. The term "non-target cleavage products" means products of a cleavage reaction that are derived from the 5' portion of the first oligonucleotide;

d. The terms “cleavage means” and “cleavage agent” refer to any means capable of cleaving the cleavage structures claimed in the ‘543 and ‘314 patents;

e. “Oligonucleotides” are not limited to nucleic acid strands containing thirty or less nucleotides;

f. In claim 1 of the ‘314 patent, the phrase “said first portion of said first target nucleic acid” in subsection (iii) refers to the “first region” of the source of target nucleic acid described in subsection (ii);

g. “Mixing” includes those conditions necessary for the oligonucleotides to anneal to the target nucleic acid and may include subjecting the mixture to the temperature cycles;

h. “Contiguous” means that there are no nucleotides in between the relevant sections or regions;

i. In the ‘543 patent, the 3' portion of the first oligonucleotide must contain a sequence complementary to the entirety of the third region of the target nucleic acid, the 5' portion of the first oligonucleotide and the 3' portion of the second oligonucleotide must contain sequences fully complementary to the entirety of the second region of the target nucleic acid, and the 5' portion of the second oligonucleotide must contain a sequence complementary to the entirety of the first region of the target nucleic acid;

j. In the ‘314 patent, at least a portion of the first oligonucleotide must be

completely complementary and annealed to the entirety of the first region and the 5' portion of the second oligonucleotide must be completely complementary and annealed to the entirety of the second region.

2. When defendant Stratagene Corporation's FullVelocity™ products are used as directed:

- a. A "cleavage means" or "cleavage agent" is provided by *Pfu* FEN-1;
- b. A "source of target nucleic acid" is provided by experimental gDNA, cDNA plasmid DNA or RNA;
- c. A "first oligonucleotide" is provided by a probe;
- d. A "second oligonucleotide" is provided by an extended primer;
- e. The probe and the extended primer "anneal" to the target nucleic acid.

3. Plaintiff's motion for summary judgment on the issue of defendant's infringement of claims 1, 5, 7, 12 and 14 of U.S. Patent No. 6,348,314 and claim 16 of plaintiff's U.S. Patent No. 6,090,543 is DENIED.

Entered this 4th day of August, 2005.

BY THE COURT:
/s/
BARBARA B. CRABB
District Judge